REMARKS

These remarks are in response to the Office Action dated March 20, 2003. Claims 1-25, 36 and 41 have been canceled. Claims 26, 37 and 39 have been amended. Support for the amended claims can be found throughout the specification. Claim 50 is allowable. No new matter has been added. Applicants wish to thank Examiners Sullivan and Falk for their helpful comments during the telephone discussion with Applicants representative on April 23, 2003.

Claims 26, 29-35, 37-40, 42-46 and 50 are pending and at issue. Applicants reserve the right to file a continuing application that includes the canceled claims. Applicants respectfully request reconsideration of the present application.

I. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 26, 29-40 and 42-46 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabling for any and all D. melanogaster comprising a transgene encoding a plurality of CAG's and at least one CAA sequence encoding a polyglutamine sequence. This rejection is moot with regard to canceled claim 36.

While Applicants respectfully traverse this rejection, Applicants note that claim 26 has been amended to recite "wherein the transgene produces polyglutamine toxicity in the transgenic D. melanogaster." In view of this amendment to claim 26, Applicants request that this rejection under 35 U.S.C. §112, first paragraph be withdrawn.

II. Rejections Under 35 U.S.C. §102(b)

Claims 37 and 39 stand rejected under 35 U.S.C. §102(b) as anticipated by Warrick et al. as evidenced by Paulson et al. because the cited reference of Warrick allegedly teaches the transgenic Drosophila claimed in the instant application. Applicants respectfully traverse this rejection as it may apply to the amended claims.

Claims 37 and 39 have been amended to recite a polyglutamine sequence "100-150," and "100-250" amino acid residues, respectively. In view of these amendments, Applicants request that this rejection be withdrawn.

III. Rejections Under 35 U.S.C. §103

Claims 1, 7, 9-14 and 17-25 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Warrick et al., in view of Rorth et al. Applicants traverse this rejection.

Applicant's maintain that this rejection is a hindsight reconstruction which uses Applicant's claim as a template to reconstruct the invention by picking and choosing isolated disclosures from the prior art. The law requires more than that.

The Examiner must show where the prior art provides a **motivation to combine** the references he has combined in the obviousness rejection. Absent a motivation to combine, obviousness has not been demonstrated. As the Federal Circuit stated in Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 934, (Fed. Cir. 1990):

> It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor.

The Office Action appears to suggest that the motivation to combine the teachings of Warrick and Rorth can be found in Warrick. For example, the Office Action states on page 6, lines 11-14, of the Office Action that "Warrick does indeed suggest the instant method…". In support of this, the Office Action points to page 948, column 1, of Warrick which recites, in part, "[w]e can now use Drosophila genetics to identify genes that delay or prevent the deleterious consequences of the polyglutamine repeat proteins on neuronal integrity." The Office Action further states on page 7, lines 2-6, of the Office Action, that "…Warrick generally teaches that Drosophila genetics can be used for the purpose of identifying genes that can delay or prevent deleterious consequences of the polyglutamine-repeat proteins. The skilled artisan would **know** (emphasis added) that this teaching encompasses the teaching of Rorth without the need for Warrick to specifically point to the teaching."

The Warrick statement (page 948, column 1, of the Warrick reference, see above), as it appears in the "Discussion" section of his publication, suggests that Drosophila genetics can be used to identify genes that modulate the effects of polyglutamine expression. However, the sentence immediately following this passage states: "Our studies with P35 indeed demonstrate that this system can effectively be used to define the genes or factors that can mitigate degeneration." Applicants note that this sentence refers to the identification of P35, an exogenous, viral-derived suppressor of apoptosis, as a suppressor of neurodegeneration in Drosophila resulting from polyglutamine toxicity.

The method used by Warrick to identify P35 as a suppressor of polyglutamine toxicity includes selecting the known P35

nucleic acid sequence for introduction in to the germline of a Drosophila and determining its effect on polyglutamine toxicity. At no point does Warrick or Rorth teach, suggest, mention or allude to any method that would involve altering the expression of an **endogenous** nucleic acid sequence to determine its effect on polyglutamine toxicity.

There are many different ways of expressing a polypeptide encoded by a nucleic acid in a cell or organism. In addition, there are many ways of modulating the activity of such expression and for determining how and when such expression is modified. With regard to polyglutamine toxicity, it is clearly desirable to try to identify those nucleic acid and polypeptide sequences that can modify conditions associated with polyglutamine expression in transgenic Drosophila. The statement by Warrick is merely a reflection of this desire. His general statement predicting that Drosophila genetics can be used to identify genes that modulate the effects of polyglutamine expression cannot make obvious all succeeding methods of accomplishing this goal using transgenic Drosophila.

Applicants acknowledge that, for the purpose of combining references, those references need not explicitly suggest combining their teachings. However, the Examiner still bears the burden of establishing a prima facie case of obviousness by showing that there is some teaching, suggestion, or motivation to **combine or modify** the teachings of the references to produce the claimed invention. Applicant's submit that the Examiner has failed to meet this burden because the rejection fails to provide reasons as to why the claimed method is obvious in view of the references. Instead, the rejection is based on a "conclusion" that the claimed method is obvious because those

skilled in the art would allegedly "know" that the teachings of Warrick encompass those of Rorth.

It is unclear to the Applicant how the skilled artisan would possess such knowledge absent something, contained in either reference, that would qualify as a teaching, a suggestion or a motivation to combine the references. Simply stating that the skilled artisan would "know" that one encompasses the other is conclusory and this conclusion is unsupported by any evidence that shows some objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, that would lead that individual to combine the relevant teachings of the references to arrive at the claimed invention.

Neither Warrick nor Rorth provide any teaching, suggestion or motivation to combine the cited references in order to arrive at a method that requires identifying an endogenous gene the expression of which is effected by the insertion of a marker sequence (see claim 1, part b). In particular, Warrick may teach a method of identifying the effect of expressing a known, non-native gene (i.e., exogenous) on polyglutamine toxicity in Drosophila, but he certainly fails to teach or suggest a method of identifying native Drosophila genes not previously associated with modulation of polyglutamine toxicity as capable of such activity. Similarly, Rorth may teach the targeted expression of endogenous nucleic acid sequences in Drosophila, but Rorth certainly fails to teach or suggest the desirability of using the method to identify sequences that can modify polyglutamine toxicity. Applicant's submit that the alleged teaching is found, not in the references of Warrick and Rorth, but in the claims being rejected. The courts have repeatedly held that the Examiner is not permitted to use the pending claims as a

blueprint for reconstructing the claimed invention from the prior art.

For the above reasons, Applicant maintains that there is no suggestion to combine the references in the manner suggested by the Examiner to achieve the claimed invention. Nevertheless, Applicants have canceled claims 1, 7, 9-14 and 17-25 in order to expedite allowance of the remaining claims. Applicants will pursue allowance of the canceled claims in a subsequently filed continuing or divisional application.

IV. REJECTIONS UNDER 35 U.S.C.§112, SECOND PARAGRAPH

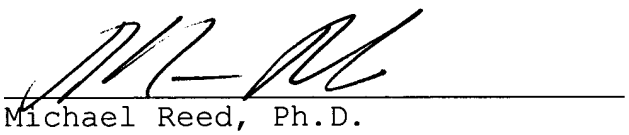
Claims 36, 37 and 39 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is moot with regard to canceled claim 36. While Applicants respectfully traverse this rejection, Applicants note that claims 37 and 39 have been amended to recite an amino acid sequence at least 100 residues in length. Applicants believe that the amendments render the rejection moot and request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

In summary, for the reasons set forth herein, Applicants maintain that claims 26, 29-35, 37-40, 42-46 and 50 clearly and patentably define the invention. Applicants request that the Examiner reconsider the various grounds set forth in the Office Action and allow the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (858) 678-5070. Please charge any fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 6/5/03



Michael Reed, Ph.D.
Reg. No. 45,647

Fish & Richardson P.C.
Customer Number: 20985
4350 La Jolla Village Drive, Suite 500
San Diego, CA 92122
Telephone: (858) 678-5070
Facsimile: (858) 678-5099